Association of Polygenic Liabilities for Major Depression, Bipolar Disorder, and Schizophrenia With Risk for Depression in the Danish Population

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Associations between polygenic liabilities for major depression, bipolar disorder and schizophrenia, and risk for depression in the Danish population

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Key Points

Question: Do polygenic liabilities for major depression (MD), bipolar disorder (BD) and schizophrenia (SZ) predict depression in the general population?

Findings: In this case-cohort study including 34,573 individuals representative of the Danish population, each 1 standard deviation increase in polygenic risk for MD was associated with a 30% increase in hazard of depression. Polygenic liabilities for SZ and BD were also associated with increased hazard of depression, but to a lesser extent.

Meaning: Polygenic risk scores trained in samples of prevalent MD cases can predict first depression in the general population.

Tweet

New study from iPSYCH shows risk for depression diagnosis in the general population increases by 30% per standard deviation increase in polygenic risk

Abstract

Importance: Although the usefulness of polygenic risk scores as a measure of genetic liability for major depression (MD) has been established, their capacity to predict who will develop depression in the general population remains relatively unexplored.

Objective: To evaluate whether polygenic risk scores for MD, bipolar disorder (BD) and schizophrenia (SZ) predict depression in the general population, and explore whether these polygenic liabilities are associated with heterogeneity in age at onset and severity at initial depression diagnosis.

Design, Setting and Participants: Participants were drawn from the Danish iPSYCH2012 case-cohort study: a representative sample drawn from the population of Denmark born between May 1, 1981 and December 31, 2005. Hazard of depression was estimated using Cox regressions modified to accommodate the case-cohort design. Case-only analyses were conducted using linear and multinomial regressions. Data analysis was conducted from February 2017 to June 2018.

Exposure: Polygenic risk scores for MD, BD and SZ trained using the most recent GWAS results from the PGC.

Main Outcome and Measures: First depressive episode (ICD-10 code F32) treated in specialty care. Severity at initial diagnosis was measured using ICD-10 code severity specifications (mild, moderate, severe without psychosis, severe with psychosis) and treatment setting (inpatient, outpatient, emergency).

Results: The sample was 51% male and included 34,573 individuals (14,799 depression cases) aged 10-31 years at censoring. Each standard deviation increase in polygenic liability for MD, BD and SZ was associated with 30% (HR=1.30, 95% CI [1.27, 1.33]), 5% (1.05, [1.02, 1.07]) and 12% (1.12, [1.09, 1.15]) increases in hazard of depression, respectively. Among cases, higher polygenic liability for BP was associated with earlier depression onset (p=.002).

Conclusions: Polygenic liability for MD predicts first depression in the general population, supporting the idea that these scores tap into an underlying liability for developing the disorder. The fact that PRS-BD and PRS-SZ also predicted depression is consistent with prior evidence that these disorders share a degree of common genetic overlap. Variation in polygenic liability may contribute slightly to heterogeneity in clinical presentation, but these effects appear minimal.

Introduction

Genes play a moderate role in the etiology of depression, with twin-based heritability estimates ranging from 30-40%[1] and SNP-based heritability estimates ranging from 9-29%.[2-4] Large empirical studies of the genetic architecture of depression indicate that it is polygenic, meaning that the contribution of genetic factors is attributable to small effects of hundreds or thousands of genetic variants spread across the genome.[3,5]

To date, multiple studies have shown small but statistically significant associations between polygenic risk scores (PRS) – a weighted sum of the number of variants associated with the disorder in a different dataset – and depression.[6-9] However, these studies focused on prevalent depression, which is more likely than incident depression to be recurrent or chronic.[10,11] Since the genome-wide association study (GWAS) data underpinning the PRSs are largely based upon prevalent cases, this could suggest that part of the genetic architecture discovered in GWAS studies is linked to chronicity or recurrence rather than the risk of developing the disorder. Therefore, while the usefulness of polygenic risk scores as a measure of genetic liability for depression has been established, their capacity to predict who will develop depression in the general population remains relatively unexplored.

In addition to heterogeneity in chronicity and recurrence, depression is also characterized by substantial variation in characteristics such as age at onset and symptom severity. Research suggests that this variation may be due at least partially to differences in genetic liability. Family studies demonstrate that individuals with a parental history of major depression (MD) are at increased risk for onset of depression at earlier ages, [12-15] and recent results from the Psychiatric Genomics Consortium (PGC) showed that polygenic risk for depression had a stronger effect on the odds of early vs. late onset

depression.[4] Research also suggests that individuals with severe MD may have a higher genetic burden than individuals with milder symptoms: A recent GWAS in Han Chinese women found an increased genetic signal among individuals with melancholia,[16] and the PGC reported higher PRSs among severe vs. moderate depression cases.[4]

Our primary aim in this study was to evaluate the extent to which polygenic liability is associated with risk for first depressive episode in the general population. As a secondary aim, we examined whether polygenic liability is associate with severity and age at onset at first depression diagnosis. Because prior evidence suggests a possible shared genetic etiology between depression and other psychiatric disorders,[2,4,17] we also examined the extent to which PRSs for bipolar disorder (BD) and schizophrenia (SZ) effect the risk for developing depression in the general population. To accomplish these aims, we used data from the iPSYCH2012 sample, a unique and powerful dataset that links genetic information with longitudinal phenotype data from Danish national registers.

Methods

Study design

For a detailed description of the iPSYCH2012 sample, see Pedersen et al.[18] Briefly, The iPSYCH2012 sample has a case-cohort design[19], which consists of two parts: a random sample (i.e. 'subcohort') of individuals drawn from a specified base population (i.e. 'full cohort') and all additional cases from the full cohort that were not selected as part of the subcohort. Like a traditional cohort study, a case-cohort study can obtain accurate estimates of hazard and risk using traditional survival analysis, provided the analyses are modified to address issues related to point and variance estimation caused by

oversampling cases.[19-22] For a more detailed description of the case-cohort design see the Supplemental Methods.

In the iPSYCH2012 sample, the subcohort consists of a random sample of 30,000 individuals drawn from the full cohort of all singletons born in Denmark between May 1, 1981 and December 31, 2005 who were alive and living in Denmark on their first birthday and had known mothers (N=1,472,762).[18] The full cohort was identified using information from the Danish Civil Registration system (DCRS).[23] The iPSYCH2012 study includes all individuals from the full cohort who were diagnosed with depression in a psychiatric hospital in Denmark between 1991 and 2012 at the age of 10 or older. Information on psychiatric diagnoses was obtained from the Danish Central Psychiatric Research Register (DCPRR).[24] Diagnoses are based on the *ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research.*[25]

Sample selection

We began by selecting all members of the subcohort and all cases outside the subcohort whose first depression diagnosis in the DCPRR was F32 – 'depressive episode'. We focused exclusively on individuals with Danish-born parents in order to reduce heterogeneity in genetic ancestry. The sample was further restricted to individuals who were successfully genotyped as part of the iPSYCH2012 sample, passed quality control (QC) measures, and were alive, living in Denmark and at least 10 years old by the end of follow up (December 31, 2012). Seventy-six individuals were removed from the subcohort because their first depression diagnosis in the register was F33 – 'recurrent depressive disorder', and we were thus unable to identify their first depressive episode. The final sample included

34,573 individuals: 20,082 members of the subcohort (of whom 308 were depression cases) and 14,491 depression cases outside the subcohort (Supplemental Figure S1).

This study was approved by the Danish Data Protection Agency. By Danish law, register-based studies do not require informed consent.

Genotyping

For a more detailed description of genotyping and quality control (QC) in the iPSYCH2012 cohort, see Pedersen et al.[18] Briefly, DNA was collected from blood spots drawn as part of routine clinical testing at birth and stored at The Danish Neonatal Screening Biobank.[26] Blood spots were located for 80,422 of the 86,189 members of the original iPSYCH2012 sample (93.3%). Genotyping was performed at the Broad Institute of Harvard and MIT (Cambridge, MA, USA) using the Infinium PsychChip v1.0 array (Illumina CA, San Diego, USA) according to the manufacturer's protocols.[27] QC and imputation (using 1000 genomes as reference panel) were conducted using the Ricopili pipeline. As the iPSYCH2012 sample is population-based, individuals from the same nuclear family unit were neither purposely sampled nor purposely removed.

Measures

Age at onset (AAO) was operationalized as the individual's age in years at first F32 diagnosis in the DCPRR. Information on severity was obtained from the ICD-10 diagnostic code: Mild (F32.0); Moderate (F32.1); Severe without psychotic features (F32.2); Severe with psychotic features (F32.3). We also examined differences in treatment setting (inpatient, emergency, outpatient) as cases treated in inpatient or emergency settings are likely more severe than cases treated in an outpatient setting.

Polygenic risk scores. PRSs were calculated using a standard approach,[28] in which an LD-pruned discovery dataset is used to identify autosomal SNPs associated with the outcome at varying p-value thresholds (p(t)), and then a score is calculated for each individual in a target dataset corresponding to the weighted sum of each subject's allelic burden at that threshold. Polygenic risk scores for MD and SZ were created using the Ricopili process with the most recently published GWAS results from the PGC (not including iPSYCH2012) as discovery datasets.[4,29] The discovery dataset for BD was comprised of leave-one-out summary statistics provided in advance of the latest GWAS publication from the BP Working Group of the PGC.[30] SNPs from the discovery datasets were filtered at INFO > 0.9 and MAF > .05, and the broad MHC-region (chr6: 25-35MB) was removed. Additionally SNPs were only included in the scores if they were reliably genotyped or imputed across all 23 waves of the iPSYCH2012 sample, at INFO > 0.6 and MAF > .01. Ten PRSs were calculated for each disorder (30 total) at the following p-value thresholds: p < .00000005; 0.000001; 0.0001; 0.001; 0.01; 0.05; 0.1; 0.2; 0.5; 1.0 (See Supplemental Table S1 for SNP numbers).[31] PRSs were standardized using the means and standard deviations from the distributions in subcohort members with Danish ancestry (N=22,182). As the iPSYCH2012 subcohort is a simple random sample drawn from the base population, the distribution of PRSs in the subcohort approximates the distribution in the Danish-born population.

Statistical analysis

Hazard of depression was estimated using Cox regressions with days since 10th birthday as the timescale. Individuals entered the analysis on their 10th birthday and were censored on the date of their first F32 diagnosis in the DCPRR, death, emigration, or December 31, 2012, whichever came first. The oldest participants were 31 years at diagnosis or censoring. We used robust standard errors and Barlow weighting to account for oversampling of cases[22,32]. All models were adjusted for sex and the top four

ancestral principal components. Additionally, all models were stratified by birth year (1981-2002) to control for secular trends in diagnostic practices and because fewer bloodspots were retrievable among individuals born in earlier years.

To examine whether polygenic liability has a stronger association with early-onset depression, we conducted separate Cox regressions, in each analysis considering as outcome only depression with onset in a specific age range. Thus, we estimated separately the association of PRSs with hazard of depression with diagnosis at ages 10-15, 16-20, 21-25 and 26-31, respectively. Likewise, we conducted separate Cox regressions considering respectively mild, moderate, severe without psychotic features, severe with psychotic features, inpatient, emergency and outpatient treatment setting at first depression as outcome in each of the analyses. We also examined the associations between PRSs, AAO and severity among cases only. Associations with age at onset in days were estimated using linear regressions. Associations with severity measures were estimated using multinomial logistic regressions. All case-only regressions were adjusted for the first 4 PCs, sex and birth year. Statistical significance was assessed at the bonferroni-corrected alpha level $p < .017$. Analyses were conducted in SAS 9.4 (See Appendix in the Supplemental Materials for SAS code).

Results

Sample characteristics

Table 1 shows sample characteristics. Non-cases were 49% female, which was expected given that the subcohort is a representative sample of the Danish population. MD cases were 68% female, which was also expected given that the typical female to male ratio of depression in the population is 2:1.[33] AAO ranged from 10 to 31 years, with a mean of 19.1 years (SD = 4.1 years). Seventeen percent of the cases

were classified as mild, 45% as moderate, 9% as severe, 3% as psychotic and 25% had no ICD-10 severity specification. The majority (60%) were treated in an outpatient setting.

Polygenic liability and hazard of depression

For all three polygenic risk scores (PRS-MD, PRS-BD and PRS-SZ), the strength of the association increased as the stringency of the p(t) threshold decreased up to $p(t) < .05$ (Supplemental Table S2 and Supplemental Figures S2-S7). For this reason and to maintain consistency with prior research, we present results from the $p(t) < .05$ thresholds throughout the remainder of the manuscript.

Each standard deviation (SD) increase in PRS-MD was associated with a 30% increase in the hazard of depression (95% CI = 1.27-1.33; $p < .0001$). In other words, compared to an individual with average polygenic liability, an individual one SD above the population average had a 30% increased risk of depression diagnosis before age 31. The corresponding values for PRS-BD and PRS-SZ were 5% (1.02-1.07; $p < .0001$) and 12% (1.09-1.15; $p < .0001$), respectively (Table S2). Figure 1 shows the associations between PRS deciles and hazard of depression, with the bottom decile (i.e. the lowest 10% of the PRS distribution) as the reference category. Relative to individuals in the bottom decile, individuals in the top decile of PRS-MD had a hazard ratio of 2.55 (2.28-2.85; $p < .0001$). The corresponding values were 1.22 (1.10-1.36; $p < .0001$) for PRS-BD and 1.49 (1.34-1.66; $p < .0001$) for PRS-SZ (Supplemental Table S3).

AAO

As shown in Figure 2 and Table 2, the hazard of depression per SD increase in PRS-MD was slightly higher for first diagnosis between 16-20 years (1.31, 1.27-1.35) and 21-25 years (1.32, 1.27-1.38),

compared to 10-15 years (1.27, 1.22-1.33) or 26-31 years (1.24, 1.16-1.32). The effect of PRS-BD was strongest for diagnosis between ages 10-15 years (1.08, 1.04-1.12) and decreased linearly with age. PRS-SZ was also for diagnosis between 10-15 years (1.17, 1.12-1.22), but lowest for diagnosis between 21-25 years (1.08, 1.04-1.13). Case-only analyses showed small associations between higher polygenic risk scores and earlier age at onset across all scores, but only the association for PRS-BD survived correction for multiple testing (Table 3).

Severity

The effects of PRS-MD, PRS-BP and PRS-SZ were all strongest for psychotic depression (Figure 2, Table 2). Differences by severity were most pronounced for PRS-SZ (1.20, 1.09-1.32) and least pronounced for PRS-MD (1.33, 1.23-1.45). In the case-only analyses, none of the associations were statistically significant; however the association between higher PRS-SZ and increased odds of psychotic depression was suggestive (OR=1.10, 95% CI [1.00- 1.21]; p = .06) (Table 3).

The effects of PRS-MD, PRS-BD and PRS-SZ were larger for inpatient and emergency treatment, but the differences in effect size were small (Figure 2). PRS-MD was marginally associated with increased odds of emergency treatment in the case-only analyses (OR=1.05, 95% CI [1.01- 1.09]; p = .02) (Table 3).

Discussion

In this study, we found that polygenic risk scores trained using aggregated results from selected samples of prevalent, often recurrent depression cases contributed meaningfully to risk for first depression in the Danish general population. For each SD increase in polygenic liability, hazard of

depression increased by 30%. Relative to individuals in the bottom 10% of the polygenic liability distribution, the hazard of depression was 2.55 times higher among individuals in the top 10%. These results suggest that estimates of genetic liability ascertained using prevalent samples are tapping in to an underlying genetic predisposition for developing depression, not just a predisposition to maintain the disorder once it has been established. Polygenic liability for BD and SZ predicted depression to a lesser extent than PRS-MD, which supports the well-documented finding that these disorders share a degree of common genetic etiology.

The effect of polygenic liability on age at onset in this study was much smaller than prior findings from family studies would suggest. This could reflect the fact that PRSs and family background are not entirely overlapping measures of genetic risk. Previous research suggests that some, but not all, of the effect of family history of schizophrenia is mediated by polygenic risk.[34] If the same holds true for depression, the larger effects identified in family studies may be attributable to the portion of the family history effect not captured by a PRS, or possibly to increased vigilance for psychiatric disorders among multiplex families. It should also be noted that the oldest members of the iPSYCH2012 cohort were only 31 at the end of follow-up, around the median age of onset for depression.[35] As a result, the entire sample could be considered 'early onset.' It may be that more pronounced differences exist in the effects of PRS-MD on risk for depression at different points across the lifespan, but that these differences are less apparent when comparing groups of younger individuals.

We found little association between polygenic liability and greater severity at initial depression diagnosis, which is inconsistent with recent findings from the PGC[4]. In general, past studies with positive findings in this area have focused on severity measures that relate to illness course, such as

number of depressive episodes and chronicity of depressive symptoms[36-38]. It could be that polygenic liability has less of an impact on characteristics of the first depressive episode than it does on characteristics of course.

It has been suggested previously that stratifying on the phenotype may be a viable method to increase statistical power for identifying genetic variants associated with depression.[39] This method has been used with some success by the CONVERGE consortium, which identified a locus significantly associated with depression in Han Chinese women by selecting for highly severe, recurrent female cases[16]. Polygenic risk was also found to be differentially associated with subtypes in autism[31], bipolar disorder and schizophrenia[30]. However, for depression, greater success in gene discovery was achieved by increasing sample size at the expense of a carefully defined phenotype.[4,40] In this vein, the results of the current study indicate that the usefulness of further stratification on the phenotype for gene discovery in depression might be more limited than we may have wished.

We found some evidence of genetic heterogeneity among depression cases in terms of polygenic liabilities for BD and SZ: there was a suggestive (although not significant) association between PRS-SZ and depression with psychotic symptoms, which makes intuitive sense. PRS-BD was significantly associated with earlier age at MD onset in the case-only analyses, and the case-cohort analyses in separate age groups suggest that PRS-BD and PRS-SZ may be particularly elevated among individuals diagnosed with MD between the ages of 10-15. These results are consistent with past studies[41,42] and could suggest that a person's degree of genetic liability for BD or SZ may place them at increased risk for different clinical manifestations of depression. However, psychiatric diagnoses are often unstable over time, and both early age at onset and greater severity/psychotic symptoms are robust risk factors

for converting to BD or SZ.[43-45] It is therefore possible that these results reflect the fact that many individuals with BD and SZ receive a depression diagnosis during the early stages of their illness.

Strengths and Limitations

The iPSYCH2012 sample has many strengths, including large sample size, population-based sampling and a uniform case definition. The fact that cases were identified through clinical records rather than selected specifically for research increases the relevance for clinical practice. In addition, the ancestral homogeneity of the Danish population reduces the likelihood of confounding by population stratification.

It should be noted, however, that although cases in the iPSYCH2012 sample are representative of individuals who received treatment for depression in psychiatric hospitals, they do not include depression cases who are untreated or only treated by general practitioners[46,47]. To put this into perspective, currently unpublished results show that the majority (85%) of individuals treated for depression in Denmark are treated first by their primary care doctors, though this proportion was lower in younger age groups.[48] The cases in the iPSYCH2012 sample therefore represent the severe end of the depression distribution in Denmark, which is both a strength and a limitation. Severe cases are likely enriched for genetic determinants[16], however the results may not generalize to milder forms of depression, and they could be biased towards the null due to misclassification. Additionally, there might be too little variation in severity to assess the effect of polygenic liability on severity in this sample. The analyses may also be subject to selection bias, if specialty-treated depression cases are more likely than untreated or primary-care treated cases to experience recurrent episodes. It is also worth noting that because we focused exclusively on first depression, we did not account for

subsequent diagnostic conversions to BD or SZ. Individuals who convert may have different genetic profiles; however there was no way to account for this without conditioning on the future, which can introduce bias.[49] Further research is needed to investigate the impact of polygenic liability on characteristics of course and outcome, including progression to other psychiatric disorders. Finally, the discovery datasets used to create the polygenic risk scores for MD, BD and SZ had different sample sizes, which impacts their statistical power.[50]

Conclusions

In conclusion, we found that polygenic liability predicts depression in the general Danish population. Polygenic liabilities for BD and SZ also predicted depression, which supports the idea that there is a shared genetic predisposition across these disorders. Heterogeneity in age at onset might be partially attributable to underlying genetic differences among depression cases, but these effects appear minimal.

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Access to Data and Data Analysis: Dr. Musliner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1

Sample characteristics

	Case status			
	Non-case		Case	
	N	*%*	*N*	*%*
Sex				
Male	10,115	51.15	4,743	32.05
Female	9,659	48.85	10,056	67.95
Age at depression diagnosis				
Non-case	19,774	100.00	-	-
10-15 years	-	-	2,965	20.04
16-20 years	-	-	6,653	44.96
21-25 years	-	-	3,981	26.90
26-31 years	-	-	1,200	8.11
ICD-10 severity specifier				
Non-case	19,774	100.00	-	-
Mild	-	-	2,573	17.39
Moderate	-	-	6,635	44.83
Severe without psychotic symptoms	-	-	1,386	9.37
Severe with psychotic symptoms	-	-	481	3.25
Severity unspecified	-	-	3,724	25.16
Treatment setting				
Non-case	19,774	100.00	-	-
Outpatient	-	-	8,880	60.00
Inpatient	-	-	2,269	15.33
Emergency	-	-	3,650	24.66
Total sample	19,774	100.00	14,799	100.00

Table 2

Associations between PRS-MD, PRS-BD and PRS-SZ and hazard of depression within different age at onset and severity subgroups

		MD		*BD*		*SZ*	
		HR (95% CI)	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Age at depression diagnosis	10-15	1.27 (1.22, 1.33)	<.0001	1.08 (1.04, 1.12)	0.0002	1.17 (1.12, 1.22)	<.0001
	16-20	1.31 (1.27, 1.35)	<.0001	1.04 (1.01, 1.07)	0.008	1.12 (1.09, 1.16)	<.0001
	21-25	1.32 (1.27, 1.38)	<.0001	1.04 (1.00, 1.08)	0.05	1.08 (1.04, 1.13)	0.0001
	26-31	1.24 (1.16, 1.32)	<.0001	1.02 (0.95, 1.10)	0.55	1.12 (1.04, 1.19)	0.0018
ICD-10 severity specifier	Mild	1.31 (1.26, 1.37)	<.0001	1.06 (1.02, 1.11)	0.005	1.09 (1.04, 1.14)	0.0002
	Moderate	1.31 (1.27, 1.35)	<.0001	1.03 (1.00, 1.06)	0.04	1.13 (1.10, 1.17)	<.0001
	Severe	1.24 (1.18, 1.32)	<.0001	1.08 (1.02, 1.14)	0.009	1.11 (1.05, 1.18)	0.0004
	Psychotic	1.33 (1.23, 1.45)	<.0001	1.13 (1.03, 1.24)	0.01	1.20 (1.09, 1.32)	<.0001
	Unspecified	1.30 (1.25, 1.35)	<.0001	1.04 (1.01, 1.08)	0.02	1.11 (1.07, 1.15)	<.0001
Treatment setting	Emergency	1.34 (1.29, 1.39)	<.0001	1.07 (1.03, 1.11)	0.001	1.14 (1.10, 1.18)	<.0001
	Inpatient	1.33 (1.27, 1.39)	<.0001	1.06 (1.01, 1.11)	0.01	1.13 (1.08, 1.18)	<.0001
	Outpatient	1.28 (1.24, 1.32)	<.0001	1.04 (1.01, 1.07)	0.008	1.11 (1.08, 1.14)	<.0001

MD = major depression, BD = bipolar disorder, SZ = schizophrenia, HR = hazard ratio, 95% CI = 95% confidence interval.

Table 3

Case-only analyses of the effects of PRS-MD, PRS-BD and PRS-SZ on age at onset and severity at first depression diagnosis

		MD				*BD*				*SZ*			
		β	*SE*	*OR (95% CI)*	*p*	*β*	*SE*	*OR (95% CI)*	*p*	*β*	*SE*	*OR (95% CI)*	*p*
Age at depression diagnosis		-0.05	0.02	.	0.04	-0.07	0.02	.	0.002	-0.05	0.02	.	0.04
ICD-10 severity specifier	Mild	----- reference category -----											
	Moderate	-0.00	0.02	1.00 (0.95,1.05)	0.99	-0.03	0.02	0.97 (0.93,1.02)	0.24	0.04	0.02	1.04 (0.99,1.09)	0.08
	Severe	-0.05	0.03	0.95 (0.89,1.01)	0.13	0.02	0.03	1.02 (0.95,1.08)	0.62	0.02	0.03	1.02 (0.95,1.09)	0.58
	Psychotic	0.02	0.05	1.02 (0.92, 1.12)	0.71	0.06	0.05	1.06 (0.97, 1.17)	0.21	0.09	0.05	1.10 (1.00, 1.21)	0.06
	Unspecified	-0.01	0.03	0.99 (0.94, 1.04)	0.77	-0.02	0.03	0.98 (0.93, 1.03)	0.48	0.02	0.03	1.02 (0.97, 1.07)	0.51
Treatment setting	Outpatient	----- reference category -----											
	Emergency	0.05	0.02	1.05 (1.01,1.09)	0.02	0.03	0.02	1.03 (0.99,1.07)	0.18	0.03	0.02	1.03 (0.99,1.07)	0.13
	Inpatient	0.04	0.02	1.04 (0.99,1.09)	0.13	0.02	0.02	1.02 (0.98,1.07)	0.37	0.02	0.02	1.02 (0.97,1.07)	0.46

MD = major depression, BD = bipolar disorder, SZ = schizophrenia, OR = odds ratio, 95% CI = 95% confidence interval.

Figure 1

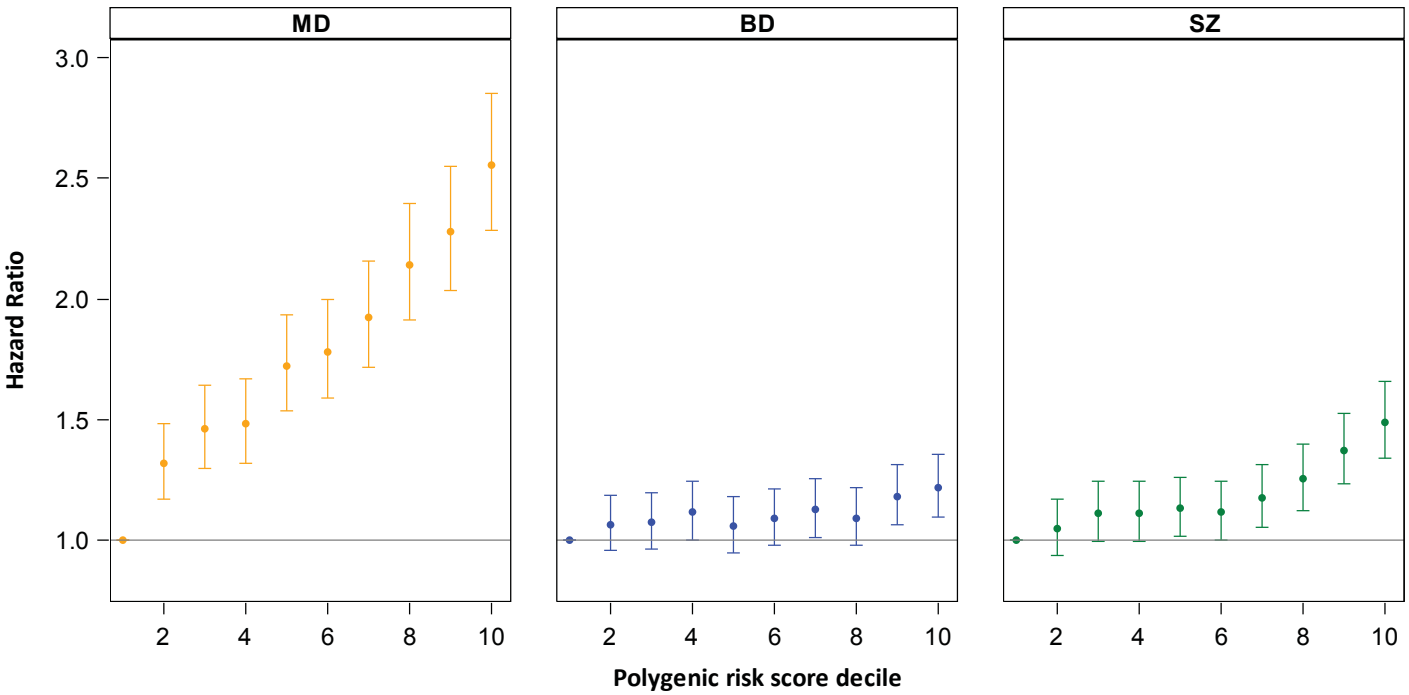
Title: Polygenic liability for MD, BD and SZ and hazard of depression in the iPSYCH2012 cohort

Explanatory legend: Hazard of depression for each decile of polygenic liability relative to the bottom decile (i.e. the bottom 10% of the polygenic liability in the Danish population). Bars represent 95% confidence intervals. MD = major depressive disorder, BD = bipolar disorder, SZ = schizophrenia.

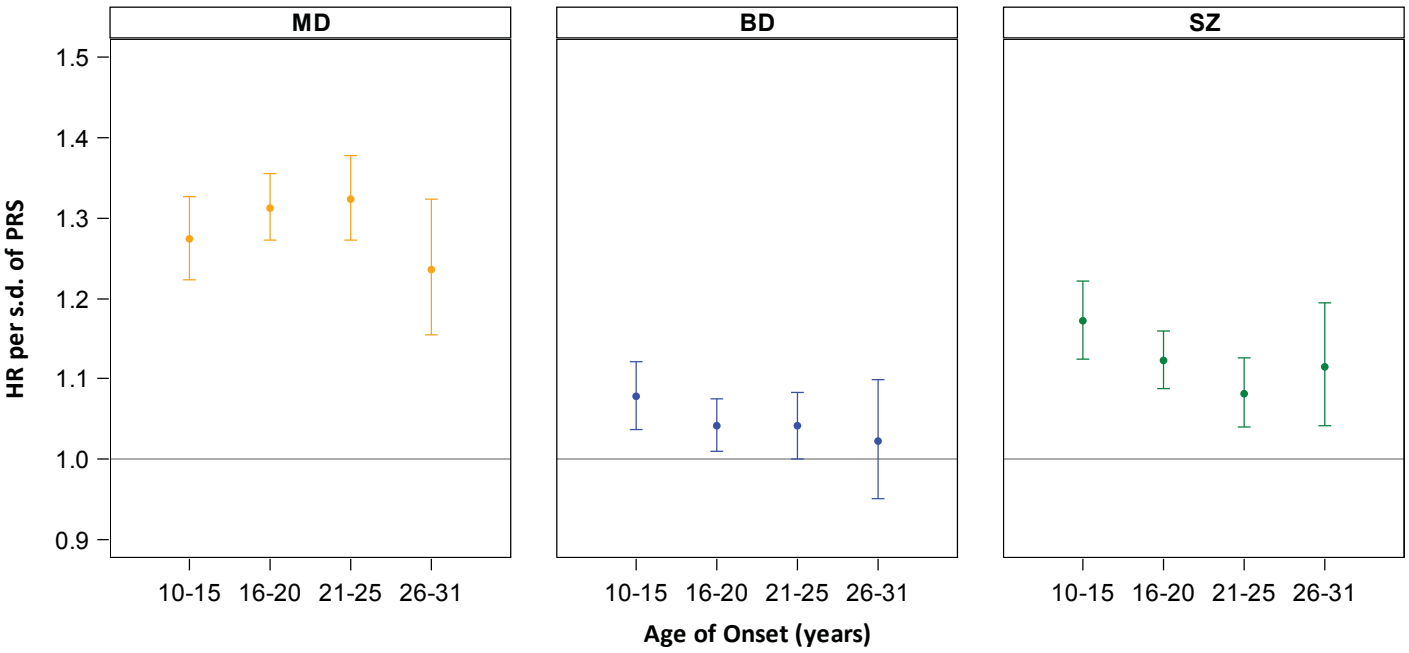
Figure 2

Title: Polygenic liability for MD, BD and SZ and hazard of depression by age and severity

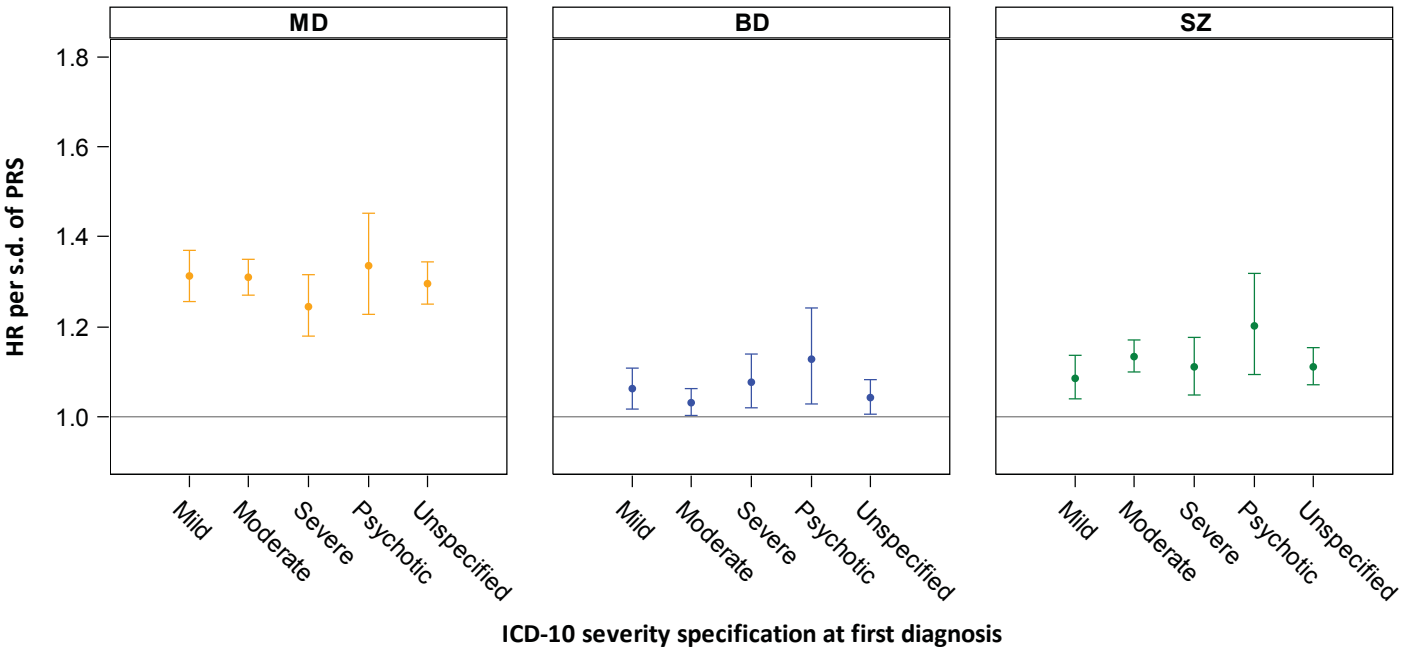
Explanatory legend: (A) Hazard ratios per standard deviation (SD) increase in polygenic liabilities for MD, BD and SZ for depression diagnosis within different age ranges. (B) Hazard ratios per SD increase in polygenic liabilities for MD, BD and SZ for depression diagnosis with different ICD-10 severity specifications. (C) Hazard ratios per SD increase in polygenic liabilities for MD, BD and SZ for depression diagnosis within different treatment settings. Bars represent 95% confidence intervals. MD = major depressive disorder, BD = bipolar disorder, SZ = schizophrenia.


MD
BD
SZ
Hazard Ratio
3.0
2.5
2.0
1.5
1.0
2
4
6
8
10
Polygenic risk score decile

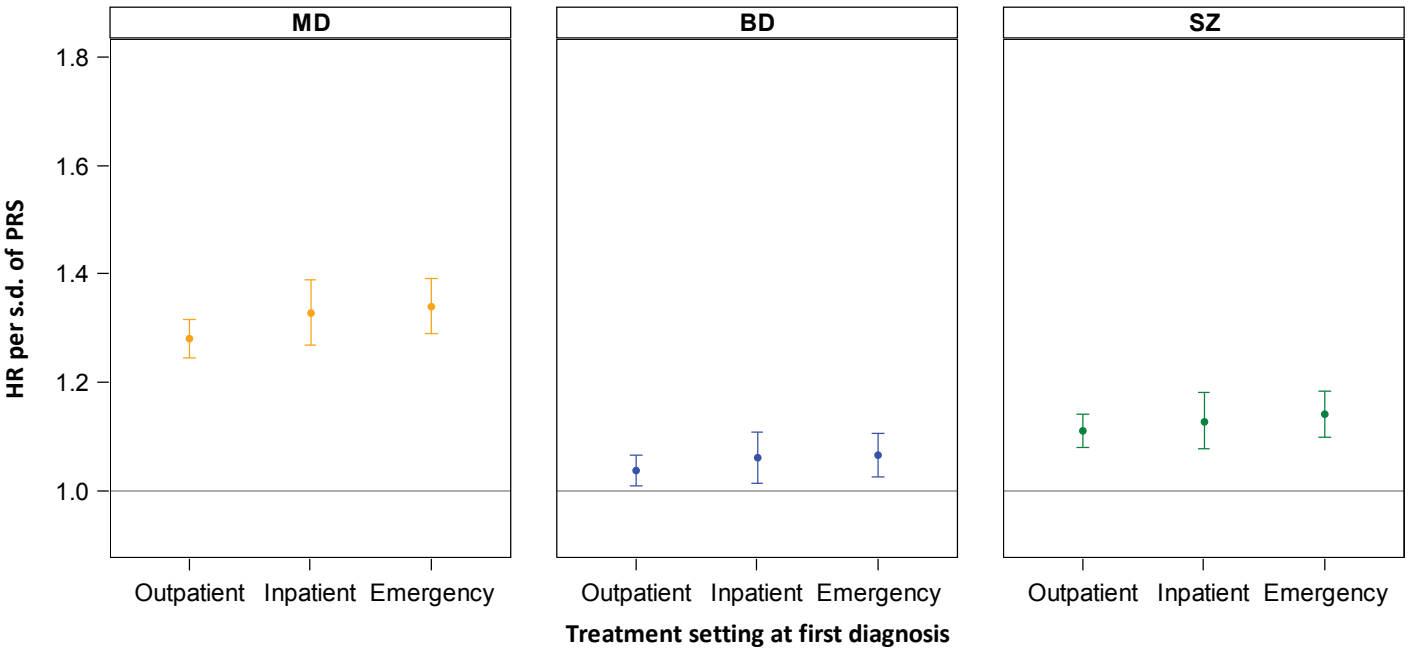
(A)


MD
BD
SZ
HR per s.d. of PRS
1.5
1.4
1.3
1.2
1.1
1.0
0.9
10-15
16-20
21-25
26-31
Age of Onset (years)

(B)


MD
BD
SZ
HR per s.d. of PRS
1.8
1.6
1.4
1.2
1.0
Mild
Moderate
Severe
Psychotic
Unspecified
ICD-10 severity specification at first diagnosis

(C)


MD
BD
SZ
HR per s.d. of PRS
1.8
1.6
1.4
1.2
1.0
Outpatient
Inpatient
Emergency
Treatment setting at first diagnosis